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(71) Applicant (for all designated States except US): **ALTANA PHARMA AG [DE/DE]; Byk-Gulden-Str. 2, 78467 Konstanz (DE).**

(72) Inventors (for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BG, BR, BW, BY, BZ, CH, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, FR, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, SZ, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW only): **HATZELMANN, Armin; Alter Wall 3, 78467 Konstanz (DE). BARSIG, Johannes; Bleichenweg 11, 78467 Konstanz (DE). MARX, Degenhard; Obere Reute 15, 78345 Moos (DE). KLEY, Hans-Peter; Im Weinberg 3b, 78476 Allensbach (DE). CHRISTIAANS, Johannes A. M.; Zevenwouden 233, NL-3524 CR UTRECHT (NL). MENGE, Wiro M. P. B.; Pontanuslaan 11, NL-6821 HM ARNHEM (NL).**

(72) Inventor; and

(75) Inventor/Applicant (for US only): **STERK, Geert Jan [NL/NL]; Stadhouderslaan 38, NL-3583 JJ UTRECHT (NL).**

(74) Agents: **WILD, Robert et al.; c/o ALTANA Pharma AG, 78467 Konstanz (DE).**

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(54) Title: PHTHALAZINONE-DERIVATIVES AS PDE4 INHIBITORS

(57) Abstract: The compounds of a certain formula (1), in which R1, R2, R3, R9 and n have the meanings as given in the description, are novel effective PDE4 inhibitors.

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PHTHALAZINONE DERIVATIVES AS PDE4 INHIBITORS

Field of application of the invention

The invention relates to novel phthalazinone-derivatives, which are used in the pharmaceutical industry for the production of pharmaceutical compositions.

Known technical background

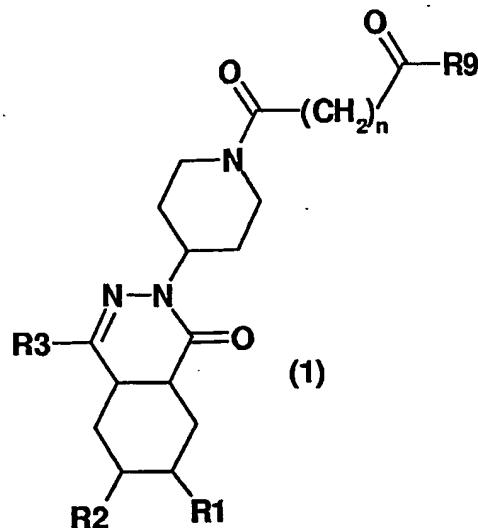
International Patent Applications WO98/31674 (= USP 6,103,718), WO99/31071, WO99/31090, WO99/47505 (= USP 6,255,303), WO01/19818, WO01/30766, WO01/30777, WO01/94319, WO02/064584, WO02/085885 and WO02/085906 disclose phthalazinone derivatives having PDE4 inhibitory properties. In the International Patent Application WO03/032993, the European Patent Applications EP 539806, EP 618201, EP 723962, EP 738715, EP 763534 and in the German Patent Application DE19604388 arylalkyl-diazinone and thiadiazinone derivatives are described as PDE4 inhibitors. International Patent Application WO93/07146 (= USP 5,716,954) discloses benzo and pyrido pyridazinone and pyridazinthione compounds with PDE4 inhibiting activity.

In the Journal of Medicinal Chemistry, Vol. 33, No. 6, 1990, pp. 1735-1741 1,4-Bis(3-oxo-2,3-dihydro-pyridazin-6-yl)benzene derivatives are described as potent phosphodiesterase inhibitors and inodilators. In the Journal of Medicinal Chemistry Vol. 45 No.12, 2002, pp. 2520-2525, 2526-2533 and in Vol. 44, No. 16, 2001, pp. 2511-2522 and pp. 2523-2535 phthalazinone derivatives are described as selective PDE4 inhibitors.

Description of the invention

It has now been found that the phthalazinone-derivatives, which are described in greater details below, have surprising and particularly advantageous properties.

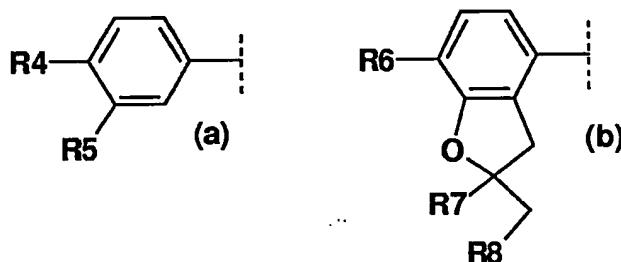
The invention thus relates to compounds of formula 1



in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely
or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom.

R9 is hydroxyl, 1-4C-alkoxy, -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,

R10 is hydroxyl, 1-4C-alkoxy or 1-4C-alkoxy-2-4C-alkyl,

R11 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R12 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,
 R13 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,
 R14 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,
 or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



wherein

A is O, S, SO, SO₂ or NR15,
 R15 is hydrogen, 1-4C-alkyl, phenyl, pyridyl, -(CH₂)_m-R16 or -(CH₂)_p-C(O)R17,
 R16 is -N(R18)R19,
 R17 is -N(R20)R21,
 R18 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,
 R19 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,
 or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-, 4-morpholinyl-, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring,
 R20 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,
 R21 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,
 or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-, 4-morpholinyl-, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring,
 n is 0, 2, 3 or 4,
 m is 2, 3 or 4,
 p is 1, 2, 3 or 4,
 and the salts of these compounds.

1-4C-Alkyl is a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

1-4C-Alkoxy is a radical which, in addition to the oxygen atom, contains a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Alkoxy radicals having 1 to 4 carbon atoms which may be mentioned in this context are, for example, the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, iso-propoxy, ethoxy and methoxy radicals.

1-8C-Alkoxy is a radical which, in addition to the oxygen atom, contains a straight-chain or branched alkyl radical having 1 to 8 carbon atoms. Alkoxy radicals having 1 to 8 carbon atoms which may be men-

tioned in this context are, for example, the octyloxy, heptyloxy, isoheptyloxy (5-methylhexyloxy), hexyloxy, isohexyloxy (4-methylpentyloxy), neohexyloxy (3,3-dimethylbutoxy), pentyloxy, isopentyloxy (3-methylbutoxy), neopentyloxy (2,2-dimethylpropoxy), butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals.

1-4C-Alkoxy which is completely or predominantly substituted by fluorine is, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and the difluoromethoxy radical, of which the difluoromethoxy radical is preferred. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy group are replaced by fluorine atoms.

3-7C-Cycloalkoxy stands for cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy or cycloheptyloxy, of which cyclopropyloxy, cyclobutyloxy and cyclopentyloxy are preferred.

3-7C-Cycloalkylmethoxy stands for cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy or cycloheptylmethoxy, of which cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy are preferred.

3-5C-Cycloalkoxy stands for cyclopropyloxy, cyclobutyloxy or cyclopentyloxy.

3-5C-Cycloalkylmethoxy stands for cyclopropylmethoxy, cyclobutylmethoxy or cyclopentylmethoxy.

As spiro-linked 5-, 6- or 7-membered hydrocarbon rings, optionally interrupted by an oxygen or sulphur atom, may be mentioned the cyclopentane, cyclohexane, cycloheptane, tetrahydrofuran, tetrahydropyran and the tetrahydrothiophen ring.

3-7C-Cycloalkyl stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, of which cyclopropyl and cyclopentyl are preferred.

3-7C-Cycloalkylmethyl stands for cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl or cycloheptylmethyl.

1-4C-Alkoxy-2-4C-alkyl stands for one a 2-4C-alkyl radical, which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the methoxyethyl and the methoxypropyl radical.

If n is zero, the group $-(CH_2)_n-$ represents a bond.

If R1 and R2 together form an additional bond, then there is between the two carbon atoms to which R1 and R2 are attached a double bond.

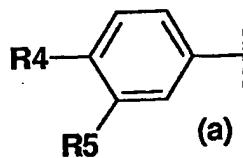
Suitable salts for compounds of formula 1 are - depending on substitution - all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being employed in salt preparation. - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are - depending on substitution - also suitable. As examples of salts with bases are mentioned the lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, here, too, the bases being employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

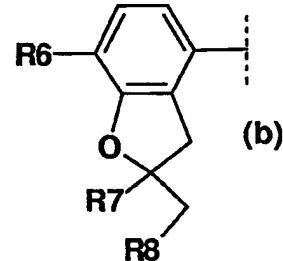
Pharmacologically intolerable salts, which can be obtained, for example, as process products during the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

According to expert's knowledge the compounds of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula 1 as well as all solvates and in particular all hydrates of the salts of the compounds of formula 1.

An embodiment (embodiment A) of the compounds of formula 1 are those in which R1 and R2 are both hydrogen or together form an additional bond, R3 represents a phenyl derivative of formulae (a) or (b)



(a)



(b)

wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
 R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is hydroxyl, 1-4C-alkoxy, -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,

R10 is hydroxyl, 1-4C-alkoxy or 1-4C-alkoxy-2-4C-alkyl,

R11 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

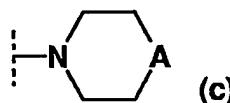
R12 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R13 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R14 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



(c)

wherein

A is O, S, SO, SO₂ or NR15,

R15 is hydrogen, 1-4C-alkyl, phenyl, pyridyl, -(CH₂)_m-R16 or -(CH₂)_p-C(O)R17,

R16 is -N(R18)R19,

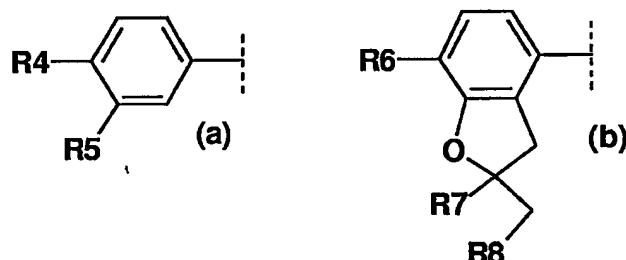
R17 is -N(R20)R21,

R18 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R19 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-, 4-morpholinyl-, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring, R20 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl, R21 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl, or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-, 4-morpholinyl-, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring, n is 2, 3 or 4, m is 2, 3 or 4, p is 1, 2, 3 or 4, and the salts of these compounds.

Compounds of formula 1 of embodiment A to be emphasized are those in which R1 and R2 are both hydrogen or together form an additional bond, R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,
 R5 is 1-4C-alkoxy,
 R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,
 R7 is methyl and
 R8 is hydrogen,
 or wherein
 R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,
 R9 is hydroxyl, 1-4C-alkoxy, -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,
 R10 is hydroxyl or 1-4C-alkoxy,
 R11 is hydrogen or 1-4C-alkyl,
 R12 is hydrogen or 1-4C-alkyl,
 R13 and R14 are identical and are hydrogen or 1-4C-alkyl,

or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



wherein

A is O, S or NR15,

R15 is hydrogen, 1-4C-alkyl or $-(CH_2)_p-C(O)R17$,

R17 is $-N(R20)R21$,

R20 is hydrogen or 1-4C-alkyl,

R21 is hydrogen or 1-4C-alkyl,

or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-, 4-morpholinyl or 4-thiomorpholinyl-ring,

n is 2,

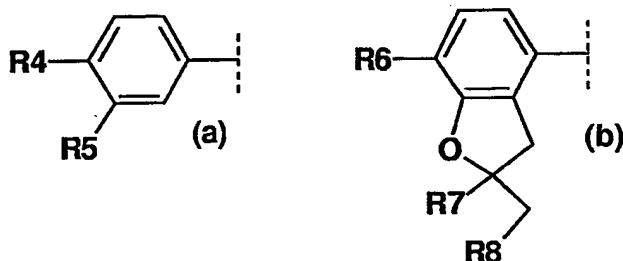
p is 1,

and the salts of these compounds.

Compounds of formula 1 of embodiment A particularly to be emphasized are those in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring.

R9 is $-N(R10)H$, $-N(H)N(R11)R12$ or $-N(R13)R14$,

R10 is hydroxyl or 1-4C-alkoxy,

R11 is hydrogen or 1-4C-alkyl,

R12 is hydrogen or 1-4C-alkyl,

R13 and R14 are identical and are hydrogen or 1-4C-alkyl,

or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



wherein

A is O, S or NR15,

R15 is hydrogen, 1-4C-alkyl or $-(CH_2)_p-C(O)R17$,

R17 is $-N(R20)R21$,

R20 is hydrogen or 1-4C-alkyl,

R21 is hydrogen or 1-4C-alkyl,

or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-, 4-morpholinyl or 4-thiomorpholinyl-ring,

n is 2,

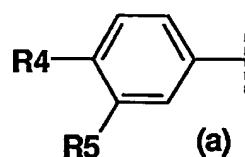
p is 1,

and the salts of these compounds.

Preferred compounds of formula 1 of embodiment A are those in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formula (a)



wherein

R4 is methoxy or ethoxy,

R5 is methoxy or ethoxy,

R9 is $-N(R13)R14$,

R13 is hydrogen,

R14 is hydrogen,

or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a ring of formula (c),



wherein

A is O or NR15,

R15 is methyl or $-(CH_2)_p-C(O)R17$,

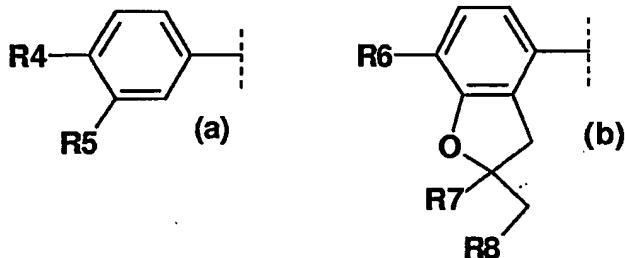
R17 is 1-pyrrolidinyl,

n is 2,

p is 1,

and the salts of these compounds.

Another embodiment (embodiment B) of the compounds of formula 1 are those in which R1 and R2 are both hydrogen or together form an additional bond, R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is 1-4C-alkoxy, $-N(R10)H$, $-N(H)N(R11)R12$ or $-N(R13)R14$,

R10 is hydroxyl, 1-4C-alkoxy or 1-4C-alkoxy-2-4C-alkyl,

R11 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R12 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,
 R13 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,
 R14 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,
 or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



wherein

A is O, S, SO, SO₂ or NR15,

R15 is hydrogen, 1-4C-alkyl, phenyl, pyridyl, -(CH₂)_m-R16 or -(CH₂)_p-C(O)R17,

R16 is -N(R18)R19,

R17 is -N(R20)R21,

R18 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R19 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-,

4-morpholinyl-, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring,

R20 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R21 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-,

4-morpholinyl, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring,

n is 0, 2, 3 or 4,

m is 2, 3 or 4,

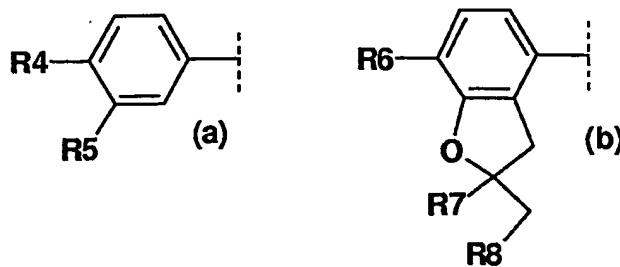
p is 1, 2, 3 or 4,

and the salts of these compounds.

Compounds of formula 1 of embodiment B to be emphasized are those in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is 1-4C-alkoxy, -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,

R10 is hydroxyl, 1-4C-alkoxy or 1-4C-alkoxy-2-4C-alkyl,

R11 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R12 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R13 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R14 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



wherein

A is O, S, SO, SO₂ or NR15,

R15 is hydrogen, 1-4C-alkyl, phenyl, pyridyl, -(CH₂)_m-R16 or -(CH₂)_p-C(O)R17,

R16 is -N(R18)R19,

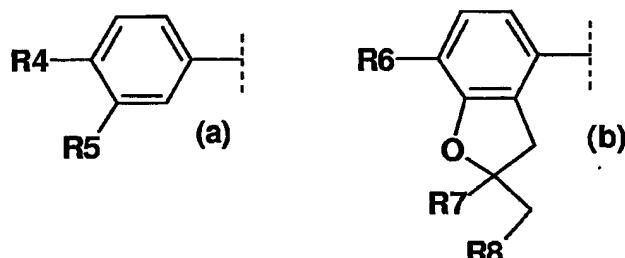
R17 is -N(R20)R21,

R18 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R19 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-, 4-morpholinyl-, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring, R20 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl, R21 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl, or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-, 4-morpholinyl-, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring, n is 2, 3 or 4, m is 2, 3 or 4, p is 1, 2, 3 or 4, and the salts of these compounds:

Compounds of formula 1 of embodiment B particularly to be emphasized are those in which R1 and R2 are both hydrogen or together form an additional bond, R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,
 R5 is 1-4C-alkoxy,
 R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,
 R7 is methyl and
 R8 is hydrogen,
 or wherein
 R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,
 R9 is 1-4C-alkoxy, -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,
 R10 is hydroxyl or 1-4C-alkoxy,
 R11 is hydrogen or 1-4C-alkyl,
 R12 is hydrogen or 1-4C-alkyl,
 R13 and R14 are identical and are hydrogen or 1-4C-alkyl,

or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



wherein

A is O, S or NR15,

R15 is hydrogen, 1-4C-alkyl or $-(CH_2)_p-C(O)R17$,

R17 is $-N(R20)R21$,

R20 is hydrogen or 1-4C-alkyl,

R21 is hydrogen or 1-4C-alkyl,

or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-, 4-morpholinyl or 4-thiomorpholinyl-ring,

n is 2,

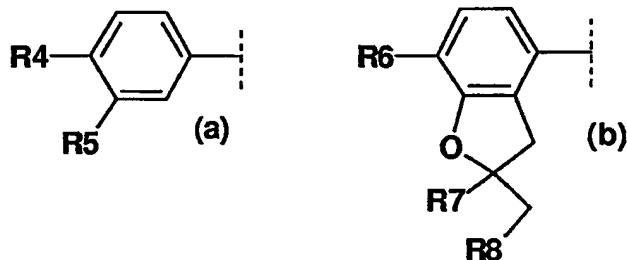
p is 1,

and the salts of these compounds.

Another embodiment (embodiment C) of the compounds of formula 1 are those in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is hydroxyl, 1-4C-alkoxy, -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,

R10 is hydroxyl, 1-4C-alkoxy or 1-4C-alkoxy-2-4C-alkyl,

R11 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R12 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R13 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R14 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



wherein

A is O, S, SO₂ or NR15,

R15 is hydrogen, 1-4C-alkyl, phenyl, pyridyl, -(CH₂)_m-R16 or -(CH₂)_pC(O)R17,

R16 is -N(R18)R19,

R17 is -N(R20)R21,

R18 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R19 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-,

4-morpholinyl-, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring,

R20 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R21 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-,

4-morpholinyl, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring,

n is 0,

m is 2, 3 or 4,

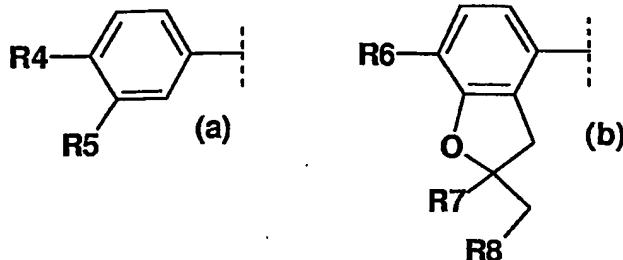
p is 1, 2, 3 or 4,

and the salts of these compounds.

Compounds of formula 1 of embodiment C to be emphasized are those in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,

R9 is hydroxyl, 1-4C-alkoxy, -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,

R10 is hydroxyl, 1-4C-alkoxy or 1-4C-alkoxy-2-4C-alkyl,

R11 is hydrogen or 1-4C-alkyl,

R12 is hydrogen or 1-4C-alkyl,

R13 is hydrogen or 1-4C-alkyl,

R14 is hydrogen or 1-4C-alkyl,

or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



wherein

A is O, S or NR15,

R15 is hydrogen, 1-4C-alkyl or -(CH₂)_p-C(O)R17,

R17 is -N(R20)R21,

R20 is hydrogen or 1-4C-alkyl,

R21 is hydrogen or 1-4C-alkyl,

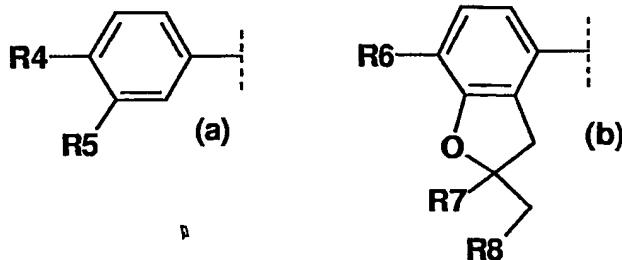
or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-, 4-morpholinyl or 4-thiomorpholinyl-ring,

n is 0,

p is 1,
and the salts of these compounds.

Compounds of formula 1 of embodiment C particularly to be emphasized are those in which R1 and R2 are both hydrogen or together form an additional bond,
R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,
R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,

R9 is -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,

R10 is hydroxyl, 1-4C-alkoxy or 1-4C-alkoxy-2-4C-alkyl,

R11 is hydrogen or 1-4C-alkyl,

R12 is hydrogen or 1-4C-alkyl,

R13 is hydrogen or 1-4C-alkyl,

R14 is hydrogen or 1-4C-alkyl,

or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



wherein

A is O, S or NR15,

R15 is hydrogen, 1-4C-alkyl or -(CH₂)_p-C(O)R17,

R17 is -N(R20)R21,

R20 is hydrogen or 1-4C-alkyl,

R21 is hydrogen or 1-4C-alkyl,

or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-,

4-morpholinyl or 4-thiomorpholinyl-ring,

n is 0,

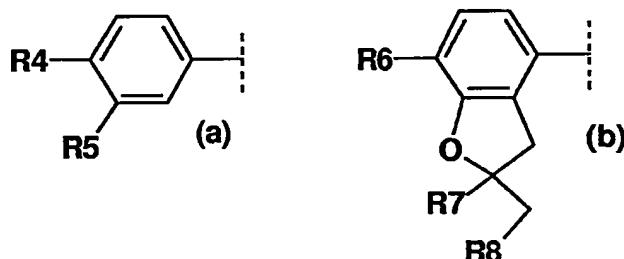
p is 1,

and the salts of these compounds.

Preferred compounds of formula 1 of embodiment C are those in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is methoxy or ethoxy,

R5 is methoxy or ethoxy,

R6 is methoxy,

R7 is methyl and

R8 is hydrogen,

R9 is -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,

R10 is hydroxyl or methoxyethyl,

R11 is methyl,

R12 is methyl,

R13 is hydrogen or methyl,

R14 is hydrogen or methyl,

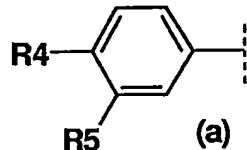
or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a ring of formula (c),



wherein

A is O or NR15,
 R15 is methyl,
 n is 0,
 and the salts of these compounds.

A subgroup of preferred compounds of formula 1 of embodiment C are those in which
 R1 and R2 are both hydrogen or together form an additional bond,
 R3 represents a phenyl derivative of formula (a)



wherein

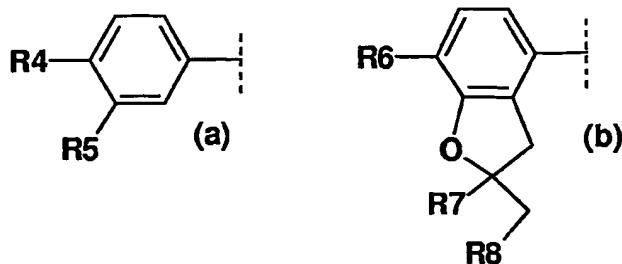
R4 is methoxy or ethoxy,
 R5 is methoxy or ethoxy,
 R9 is -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,
 R10 is hydroxyl or methoxyethyl,
 R11 is methyl,
 R12 is methyl,
 R13 is hydrogen or methyl,
 R14 is hydrogen or methyl,
 or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a ring of formula (c),



wherein

A is O or NR15,
 R15 is methyl,
 n is 0,
 and the salts of these compounds.

Particularly preferred compounds of formula 1 of embodiment C are those in which
 R1 and R2 are both hydrogen or together form an additional bond,
 R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is methoxy or ethoxy,

R5 is methoxy or ethoxy,

R6 is methoxy,

R7 is methyl and

R8 is hydrogen,

R9 is $-\text{N}(\text{R13})\text{R14}$,

R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a ring of formula (c),



wherein

A is O,

n is 0,

and the salts of these compounds.

A special embodiment of the compounds of the present invention includes those compounds of formula 1 in which R3 represents a phenyl derivative of formula (a).

Another special embodiment of the compounds of the present invention includes those compounds of formula 1 in which R3 represents a phenyl derivative of formula (a) and R4 and R5 have the meaning methoxy.

Still another special embodiment of the compounds of the present invention includes those compounds of formula 1 in which R1 and R2 are both hydrogen.

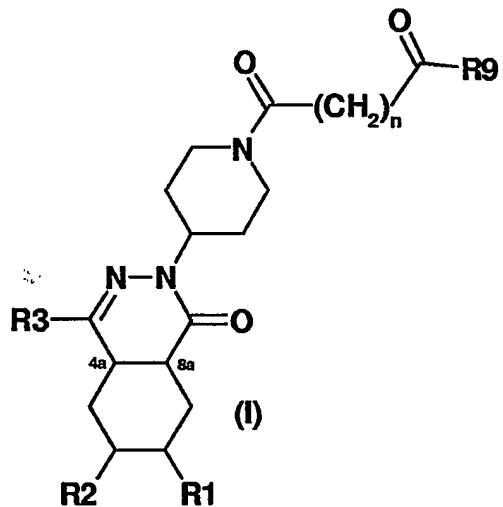
A further special embodiment of the compounds of the present invention includes those compounds of formula 1 in which R3 represents a phenyl derivative of formula (a), R4 and R5 have the meaning methoxy and n is 0.

Still a further special embodiment of the compounds of the present invention includes those compounds of formula 1 in which R3 represents a phenyl derivative of formula (a), R4 and R5 have the meaning methoxy and n is 2.

Another special embodiment of the compounds of the present invention includes those compounds of formula 1 in which R3 represents a phenyl derivative of formula (b).

The compounds of formula 1 are chiral compounds. Chiral centers exist in the compounds of formula 1 in the positions 4a and 8a. In case R3 represents a phenyl derivative of formula (b) there is one further chiral center in the dihydrofuran-ring, if the substituents -R7 and -CH₂R8 are not identical. However, preferred are in this connection those compounds, in which the substituents -R7 and -CH₂R8 are identical or together and with inclusion of the two carbon atoms to which they are bonded form a spiro-connected 5-, 6- or 7-membered hydrocarbon ring.

Numbering:



Therefore the invention includes all conceivable pure diastereomers and pure enantiomers, as well as all mixtures thereof independent from the ratio, including the racemates. Preferred are those compounds, in which the hydrogen atoms in the positions 4a and 8a are cis-configurated. Especially preferred in this connection are those compounds, in which the absolute configuration (according to the rules of Cahn, Ingold and Prelog) is S in the position 4a and R in the position 8a. Racemates can be split up into the corresponding enantiomers by methods known by a person skilled in the art. Preferably the racemic mixtures are separated into two diastereomers during the preparation with the help of an optical active separation agent on the stage of the cyclohexanecarboxylic acids or the 1,2,3,6-tetrahydrobenzoic acids (for example, starting compound A1 and A4). As separation agents may be mentioned, for example, optical active amines such as the (+)- and (-)-forms of 1-phenylethylamine [(R)-(+)-1-phenylethylamine = (R)-(+)-

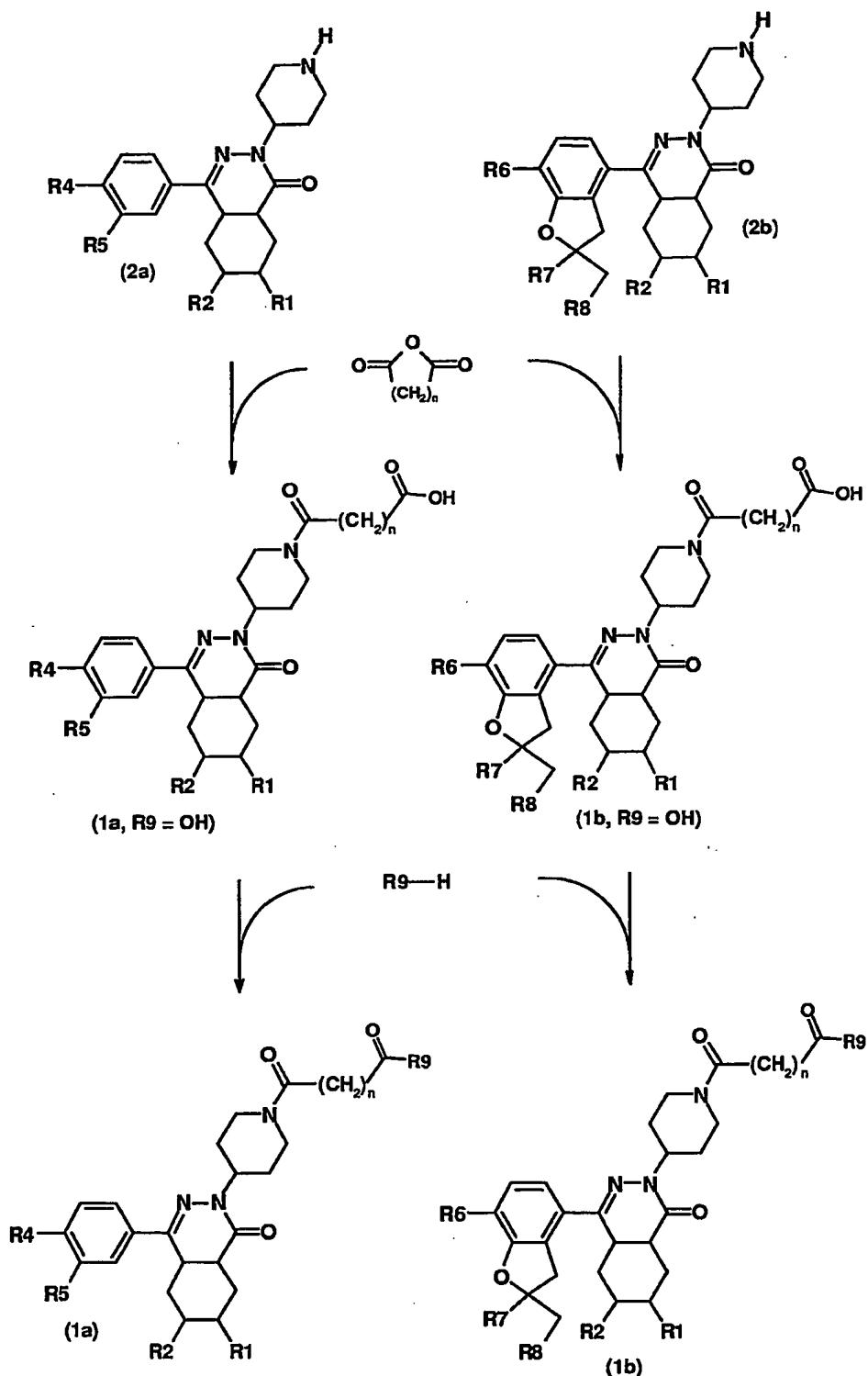
α -methylbenzylamine or (S)-(-)-1-phenylethylamine = (S)-(-)- α -methylbenzylamine) and ephedrine, the optical active alkaloids quinine, cinchonine, cinchonidine and brucine.

The compounds of formula 1 according to the invention can be prepared, for example, as described in Reaction schemes 1 and 2.

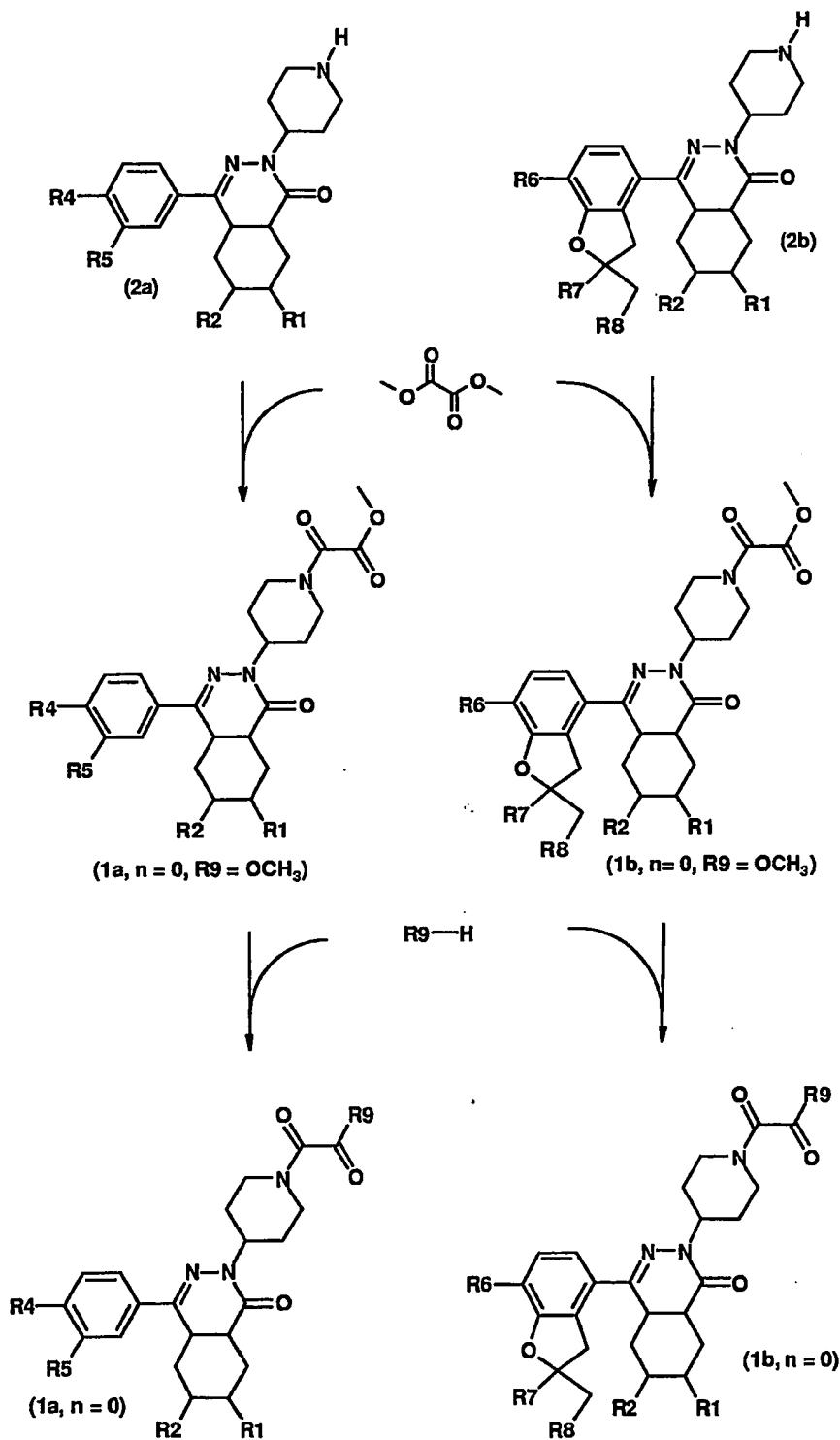
In reaction scheme 1 the preparation of compounds of formula 1 is described, in which n have the meanings 2, 3 and 4.

In reaction scheme 2 the preparation of compounds of formula 1 is described, in which n has the meaning 0.

Reaction scheme 1:



Reaction scheme 2:



In the first reaction step in reaction scheme 1 compounds of formulae 2a and 2b, in which R1, R2, R4, R5, R6, R7 and R8 have the above-mentioned meanings, are reacted with a cyclic anhydride, such as for example succinic acid anhydride or glutaric acid anhydride to yield compounds of formulae 1a or 1b, in which R1, R2, R4, R5, R6, R7 and R8 have the above-mentioned meanings, n is 2 or 3 and R9 is OH.

Alternatively, compounds of formulae 2a and 2b, in which R1, R2, R4, R5, R6, R7 and R8 have the above-mentioned meanings, are reacted with compounds of formula Cl-C(O)-(CH₂)_n-C(O)-O-(1-4C-alkyl), in which n is 2, 3 or 4, followed by saponification of the resulting ester to yield compounds of formulae 1a or 1b, in which R1, R2, R4, R5, R6, R7 and R8 have the above-mentioned meanings, n is 2, 3 or 4 and R9 is OH.

These compounds of formulae 1a and 1b, in which R1, R2, R4, R5, R6, R7 and R8 have the above-mentioned meanings, n is 2, 3 or 4 and R9 is OH, can be converted into further derivatives of formulae 1a and 1b using standard methods, known to the person skilled in the art to produce esters, amides, N-hydroxy-amides, N-alkoxy-amides or hydrazides.

Reaction scheme 2 shows an analogous synthesis for compounds of formulae 1a and 1b, in which R1, R2, R4, R5, R6, R7 and R8 have the above-mentioned meanings and n is 0.

Here, in the first reaction step dimethyl oxalate is used instead of succinic acid anhydride or glutaric acid anhydride.

Compounds of formulae 2a and 2b, in which R1, R2, R4, R5, R6, R7 and R8 have the above-mentioned meanings are known or can be prepared as described, for example, in WO02/064584.

Suitably, the conversions are carried out analogous to methods, which are familiar per se to the person skilled in the art, for example, in the manner which is described in the following examples.

The substances according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallising the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (for example a ketone like acetone, methylethylketone, or methylisobutylketone, an ether, like diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol, such as ethanol, isopropanol) which contains the desired acid, or to which the desired acid is

then added. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by basification into the free compounds which, in turn, can be converted into salts. In this manner, pharmacologically non-tolerable salts can be converted into pharmacologically tolerable salts.

The following examples illustrate the invention in greater detail, without restricting it. As well, further compounds of formula 1, of which the preparation is explicitly not described, can be prepared in an analogous way or in a way which is known by a person skilled in the art using customary preparation methods.

The compounds, which are mentioned in the examples as well as their salts are preferred compounds of the invention. In the examples, RT stands for room temperature, h for hour(s), min for minute(s) and M. p. for melting point.

Examples**Final products**

1. 4-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-4-oxo-butyric acid

A solution of 50 mmol of intermediate A1, 50 mmol of succinic anhydride and 6 ml of triethylamine in 200 ml of dichloromethane is stirred at RT. After 18 h the mixture is washed with 1N hydrochloric acid, dried over magnesium sulfate and evaporated. The title compound is crystallized from ethyl acetate.

M. p. 175-177 °C

2. 1-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-4-morpholin-4-yl-butane-1,4-dione

13 mmol of 1-diethylaminoethyl-3-ethylcarbodiimide hydrochloride are added to a solution of 10 mmol of compound 1 and 12 mmol of morpholine in 20 ml of dimethylformamide. The resulting mixture is stirred for 1 h and subsequently evaporated. The residue is dissolved in ethyl acetate and the resulting solution is washed with aqueous sodium carbonate. After drying over magnesium sulfate and evaporating, the title compound is crystallized from ethyl acetate. M. p. 144-147 °C

3. 1-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-4-(4-methyl-piperazin-1-yl)-butane-1,4-dione fumarate

Prepared from compound 1 and 1-methylpiperazine as described for compound 2. Crystallized from tetrahydrofuran as the fumarate. M. p. 95-98 °C

4. 4-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-4-oxo-butyramide

Prepared from compound 1 and 20 ml of a saturated solution of ammoniac in dichloromethane as described for compound 2. M. p. 103-105 °C

5. 1-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-4-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-piperazin-1-yl]-butane-1,4-dione fumarate

Prepared from compound 1 and 2-(piperazin-1-yl)-1-(pyrrolidin-1-yl)-ethanone as described for compound 2. Crystallized from tetrahydrofuran as the fumarate. M. p. 147-151 °C

6. 2-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-2-oxo-acetamide

A solution of 1 g of intermediate A2 in 20 ml of methanol is saturated with ammoniac and left for 18 h at RT. After evaporating the reaction mixture, the residue is crystallized from ethyl acetate.

M. p. 107-110 °C

7. 1-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-2-morpholin-4-yl-ethane-1,2-dione

A solution of 1 g of intermediate A2, 3 equivalents of morpholine and 1 ml of triethylamine in 20 ml of methanol is left for 8 h at RT. After evaporating the solution, the residue is purified by chromatography (elution with a mixture of methanol and ethyl acetate, 1/1). The title compound is crystallised from ethyl acetate. M. p. 209-211 °C

8. 1-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-2-(4-methyl-piperazin-1-yl)-ethane-1,2-dione hydrochloride

Prepared from 1 g of intermediate A2 and 1 g of 1-methylpiperazine as described for compound 7. After evaporating the reaction mixture, the residue is dissolved in ethyl acetate and this solution is washed with aqueous sodium carbonate. The ethyl acetate solution is dried over magnesium sulfate and evaporated. The residue is dissolved again in ethyl acetate and a solution of hydrochloric acid in ether is added. The precipitate is filtered off and dried. M. p. 241-244 °C

9. 2-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-N,N-dimethyl-2-oxo-acetamide

Prepared from 1 g of intermediate A2 and 5 ml a 30% solution of dimethylamine in ethanol as described for compound 6. M. p. 125-128 °C

10. 2-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-N-hydroxy-2-oxo-acetamide

Prepared from 1 g of intermediate A2 and 1 g of hydroxylamine as described for compound 8. The title compound is crystallized from ethyl acetate. M. p. 131-133 °C

11. 2-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,6,7,8a-hexahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-2-oxo-acetamide

Prepared from intermediate A5 and ammoniac as described for compound 6. M. p. 119-121 °C

12. 1-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,6,7,8a-hexahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-2-(morpholin-4-yl)-ethane-1,2-dione

Prepared from intermediate A5 and morpholine as described for compound 7. M. p. 181-183 °C

13. 1-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,6,7,8a-hexahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-2-(4-methyl-piperazin-1-yl)-ethane-1,2-dione

Prepared from intermediate A5 and 1-methylpiperazine as described for compound 7. M. p. 158-161 °C

14. [4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-2-oxo-acetic acid N,N-dimethyl-hydrazide

Prepared from intermediate A2 and N,N-dimethylhydrazine as described for compound 7. M. p. 211-215 °C

15. 2-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-N-(2-methoxy-ethyl)-2-oxo-acetamide

Prepared from intermediate A2 and 2-methoxyethylamine as described for compound 7.
M. p. 161-164 °C

Starting Compounds and Intermediates**A1. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-piperidin-4-yl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride**

A solution of 50 mmol of the salt of (S)-(-)- α -methylbenzylamine and (cis)-2-(3,4-dimethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid (starting compound A6), 55 mmol of piperidin-4-yl-hydrazine dihydrochloride and 100 mmol of triethylamine in 150 ml of 1-propanol is refluxed for 18 h. After cooling to RT, the precipitate is filtered off and dried. M. p. 285-288 °C

A2. {4-[{(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl}-2-oxo-acetic acid methyl ester

A solution of 10 g of intermediate A1, 10 ml of dimethyl oxalate and 10 ml of triethylamine is left at RT for 18 h. After evaporating the reaction mixture, the residue is dissolved in diethyl ether and this solution is washed with aqueous sodium carbonate. The organic phase is dried over magnesium sulfate and evaporated. The residue crystallizes from a mixture of diethyl ether and petroleum ether (60-80 °C).

M. p. 97-99 °C

A3. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-piperidin-4-yl-4a,5,6,7,8,8a-hexahydro-2H-phthalazin-1-one

A solution of 50 mmol of intermediate A4 in dichloromethane is washed twice with 1N sulphuric acid, dried over magnesium sulphate and evaporated. The residue is dissolved in 150 ml of ethyl acetate, 50 mmol of 4-hydrazinopiperidine dihydrochloride and 75 mmol of triethylamine is added and the resulting mixture is refluxed for 18 h. After cooling to RT, the precipitate is filtered off and dried. M. p. 291-293 °C (with decomposition).

A4. L-(-)- α -methylbenzylamine salt of (1R,2S)-2-[1-(3,4-Dimethoxy-phenyl)-methanoyl]-cyclohexanecarboxylic acid

A solution of 0.25 mole of L-(-)- α -methylbenzylamine in 100 ml of ethyl acetate is added to a solution of 0.5 mole of 2-[1-(3,4-Dimethoxy-phenyl)-methanoyl]-cyclohexanecarboxylic acid in 1.5 l of ethyl acetate. The resulting mixture is filtered off and suspended in 1 l of ethyl acetate, heated for 1 h at 60°C and filtered off while still warm. M.p. 155-157 °C

A5. {4-[{4aS,8aR}-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,6,7,8,8a-hexahydro-1H-phthalazin-2-yl]-piperidin-1-yl}-2-oxo-acetic acid methyl ester

Prepared from intermediate A3 and dimethyl oxalate as described for intermediate A2.

M. p. 140-142 °C

A6. (cis)-2-(3,4-Dimethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid

Prepared as described in WO98/31674.

A7. (cis)-2-(3,4-Dimethoxybenzoyl)cyclohexanecarboxylic acid

Prepared as described in WO98/31674.

Commercial utility

The compounds according to the invention have useful pharmacological properties which make them industrially utilizable. As selective cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4), they are suitable on the one hand as bronchial therapeutics (for the treatment of airway obstructions on account of their dilating action but also on account of their respiratory rate- or respiratory drive-increasing action) and for the removal of erectile dysfunction on account of their vascular dilating action, but on the other hand especially for the treatment of disorders, in particular of an inflammatory nature, e.g. of the airways (asthma prophylaxis), of the skin, of the intestine, of the eyes, of the CNS and of the joints, which are mediated by mediators such as histamine, PAF (platelet-activating factor); arachidonic acid derivatives such as leukotrienes and prostaglandins, cytokines, interleukins, chemokines, alpha-, beta- and gamma-interferon, tumor necrosis factor (TNF) or oxygen free radicals and proteases. In this context, the compounds according to the invention are distinguished by a low toxicity, a good enteral absorption (high bioavailability), a large therapeutic breadth and the absence of significant side effects.

On account of their PDE-inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine as therapeutics, where they can be used, for example, for the treatment and prophylaxis of the following illnesses: acute and chronic (in particular inflammatory and allergen-induced) airway disorders of varying origin (bronchitis, allergic bronchitis, bronchial asthma, emphysema, COPD); dermatoses (especially of proliferative, inflammatory and allergic type) such as psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, Lichen simplex, sunburn, pruritus in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and widespread pyodermias, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders; disorders which are based on an excessive release of TNF and leukotrienes, for example disorders of the arthritis type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic conditions), disorders of the immune system (AIDS, multiple sclerosis), graft versus host reaction, allograft rejections, types of shock (septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)) and also generalized inflammations in the gastrointestinal region (Crohn's disease and ulcerative colitis); disorders which are based on allergic and/or chronic, immunological false reactions in the region of the upper airways (pharynx, nose) and the adjacent regions (paranasal sinuses, eyes), such as allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and also nasal polyps; but also disorders of the heart which can be treated by PDE inhibitors, such as cardiac insufficiency, or disorders which can be treated on account of the tissue-relaxant action of the PDE inhibitors, such as, for example, erectile dysfunction or colics of the kidneys and of the ureters in connection with kidney stones. In addition, the compounds of the invention are useful in the treatment of diabetes insipidus, diabetes mellitus, leukaemia, osteoporosis and conditions associated with cerebral metabolic inhibition, such as cerebral senility, senile demen-

tia (Alzheimer's disease), memory impairment associated with Parkinson's disease or multiinfarct dementia; and also illnesses of the central nervous system, such as depressions or arteriosclerotic dementia.

The invention further relates to a method for the treatment of mammals, including humans, which are suffering from one of the above mentioned illnesses. The method is characterized in that a therapeutically active and pharmacologically effective and tolerable amount of one or more of the compounds according to the invention is administered to the ill mammal.

The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of illnesses, especially the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of the illnesses mentioned.

The invention furthermore relates to pharmaceutical compositions for the treatment and/or prophylaxis of the illnesses mentioned, which contain one or more of the compounds according to the invention.

Additionally, the invention relates to an article of manufacture, which comprises packaging material and a pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective for antagonizing the effects of the cyclic nucleotide phosphodiesterase of type 4 (PDE4), ameliorating the symptoms of an PDE4-mediated disorder, and wherein the packaging material comprises a label or package insert which indicates that the pharmaceutical agent is useful for preventing or treating PDE4-mediated disorders, and wherein said pharmaceutical agent comprises one or more compounds of formula 1 according to the invention. The packaging material, label and package insert otherwise parallel or resemble what is generally regarded as standard packaging material, labels and package inserts for pharmaceuticals having related utilities.

The pharmaceutical compositions are prepared by processes which are known per se and familiar to the person skilled in the art. As pharmaceutical compositions, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar with auxiliaries or excipients which are suitable for the desired pharmaceutical formulations on account of his/her expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

The administration of the pharmaceutical compositions according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral delivery is preferred.

For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation in the form of an aerosol; the aerosol particles of solid, liquid or mixed composition preferably having a diameter of 0.5 to 10 μm , advantageously of 2 to 6 μm .

Aerosol generation can be carried out, for example, by pressure-driven jet atomizers or ultrasonic atomizers, but advantageously by propellant-driven metered aerosols or propellant-free administration of micronized active compounds from inhalation capsules.

Depending on the inhaler system used, in addition to the active compounds the administration forms additionally contain the required excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For the purposes of inhalation, a large number of apparatuses are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is as right as possible for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhaler described in European Patent Application EP 0 505 321), using which an optimal administration of active compound can be achieved.

For the treatment of dermatoses, the compounds according to the invention are in particular administered in the form of those pharmaceutical compositions which are suitable for topical application. For the production of the pharmaceutical compositions, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The pharmaceutical compositions according to the invention are prepared by processes known per se. The dosage of the active compounds is carried out in the order of magnitude customary for PDE inhibitors. Topical application forms (such as ointments) for the treatment of dermatoses thus contain the active compounds in a concentration of, for example, 0.1-99%. The dose for administration by inhalation is customarily between 0.1 and 3 mg per day. The customary dose in the case of systemic therapy (p.o. or i.v.) is between 0.03 and 3 mg/kg per day.

Biological investigations

The second messenger cyclic AMP (cAMP) is well-known for inhibiting inflammatory and immunocompetent cells. The PDE4 isoenzyme is broadly expressed in cells involved in the initiation and propagation of inflammatory diseases (H Tenor and C Schudt, in „Phosphodiesterase Inhibitors“, 21-40, „The Handbook of Immunopharmacology“, Academic Press, 1996), and its inhibition leads to an increase of the intracellular cAMP concentration and thus to the inhibition of cellular activation (JE Souness et al., Immunopharmacology 47: 127-162, 2000).

The antiinflammatory potential of PDE4 inhibitors *in vivo* in various animal models has been described (MM Teixeira, TIPS 18: 164-170, 1997). For the investigation of PDE4 inhibition on the cellular level (*in vitro*), a large variety of proinflammatory responses can be measured. Examples are the superoxide production of neutrophilic (C Schudt et al., Arch Pharmacol 344: 682-690, 1991) or eosinophilic (A Hatzelmann et al., Brit J Pharmacol 114: 821-831, 1995) granulocytes, which can be measured as luminol-enhanced chemiluminescence, or the synthesis of tumor necrosis factor- α in monocytes, macrophages or dendritic cells (Gantner et al., Brit J Pharmacol 121: 221-231, 1997, and Pulmonary Pharmacol Therap 12: 377-386, 1999). In addition, the immunomodulatory potential of PDE4 inhibitors is evident from the inhibition of T-cell responses like cytokine synthesis or proliferation (DM Essayan, Biochem Pharmacol 57: 965-973, 1999). Substances which inhibit the secretion of the afore-mentioned proinflammatory mediators are those which inhibit PDE4. PDE4 inhibition by the compounds according to the invention is thus a central indicator for the suppression of inflammatory processes.

Method for measuring inhibition of PDE4 activities**Method A:**

The PDE activity was determined according to Thompson et al. (Adv Cycl Nucl Res 10: 69-92, 1979) with some modifications (Bauer and Schwabe, Naunyn-Schmiedeberg's Arch Pharmacol 311: 193-198, 1980). The test samples contained 20 mM Tris (pH 7.4), 5 mM MgCl₂, 0.5 μM cAMP or cGMP, [³H]cAMP or [³H]cGMP (about 30 000 cpm/sample), the PDE isoenzyme-specific additives described in greater detail below, the indicated concentrations of inhibitor and an aliquot of the enzyme solution in a total sample volume of 200 μl. Dilution series of the compounds according to the invention were prepared in DMSO and further diluted in the samples [1:100 (v/v)], to give the desired end concentration of the inhibitors at a DMSO concentration of 1% (v/v), which for its part has only a minute effect on PDE activity.

After preincubation at 37°C for 5 minutes, the reaction was started by addition of the substrate (cAMP). The samples were incubated at 37°C for a further 15 min. The reaction was terminated by addition of 50 μl 0.2 N HCl. After cooling on ice for 10 minutes and addition of 25 μg 5'-nucleotidase (snake venom from *Crotalus atrox*), the mixture was again incubated at 37°C for 10 min and the samples were then applied to QAE Sephadex A-25 columns (sample volume 1 ml). The columns were eluted with 2 ml of 30 mM ammonium formate (pH 6.0). The radioactivity of the eluate was measured and corrected by the corresponding blank values (measured in the presence of denatured protein); the blank values were less than 5% of the total radioactivity. In no case did the proportion of hydrolyzed nucleotide exceed 30% of the original substrate concentration.

PDE4 (cAMP-specific) was investigated in the cytosol of human polymorphonuclear leukocytes (PMNL) [isolated from leukocyte concentrates, see Schudt et al., Arch Pharmacol 1991: 344, 682-690] using cAMP as substrate. The PDE3 inhibitor motapizone (1 μM) was used to suppress the PDE3 activity emanating from contaminated platelets.

The IC₅₀ values were determined from the concentration-inhibition curves by nonlinear regression.

Method B:

The PDE4B2 (GB no. M97515) was a gift of Prof. M. Conti (Stanford University, USA). It was amplified from the original plasmid (pCMV5) via PCR with primers Rb9 (5'- GCCAGCGTGCAAATAATGAAGG -3') and Rb10 (5'- AGAGGGGGATTATGTATCCAC -3') and cloned into the pCR-Bac vector (Invitrogen, Groningen, NL).

The recombinant baculovirus was prepared by means of homologous recombination in SF9 insect cells. The expression plasmids were cotransfected with Bac-N-Blue (Invitrogen, Groningen, NL) or Baculo-Gold DNA (Pharmingen, Hamburg) using a standard protocol (Pharmingen, Hamburg). Wt virus-free recombinant virus supernatants were selected using plaque assay methods. After that, high-titre virus supernatants were prepared by amplifying 3 times. PDE4B2 was expressed in SF21 cells by infecting 2×10^6 cells/ml with an MOI (multiplicity of infection) between 1 and 10 in serum-free SF900 medium (Life Technologies, Paisley, UK). The cells were cultured at 28°C for 48 – 72 hours, after which they were pelleted for 5-10 min at 1000 g and 4°C.

The SF21 insect cells were resuspended, at a concentration of approx. 10^7 cells/ml, in ice-cold (4°C) homogenization buffer (20 mM Tris, pH 8.2, containing the following additions: 140 mM NaCl, 3.8 mM KCl, 1 mM EGTA, 1 mM MgCl₂, 10 mM β-mercaptoethanol, 2 mM benzamidine, 0.4 mM Pefablock, 10 μM leupeptin, 10 μM pepstatin A, 5 μM trypsin inhibitor) and disrupted by ultrasonication. The homogenate was then centrifuged for 10 min at 1000×g and the supernatant was stored at -80°C until subsequent use (see below). The protein content was determined by the Bradford method (BioRad, Munich) using BSA as the standard.

PDE4B2 activity was inhibited by the said compounds in a modified SPA (scintillation proximity assay) test, supplied by Amersham Biosciences (see procedural instructions "phosphodiesterase [3H]cAMP SPA enzyme assay, code TRKQ 7090"), carried out in 96-well microtitre plates (MTP's). The test volume is 100 μl and contains 20 mM Tris buffer (pH 7.4), 0.1 mg of BSA (bovine serum albumin)/ml, 5 mM Mg²⁺, 0.5 μM cAMP (including about 50,000 cpm of [3H]cAMP), 1 μl of the respective substance dilution in DMSO and sufficient recombinant PDE (1000×g supernatant, see above) to ensure that 10-20% of the cAMP is converted under the said experimental conditions. The final concentration of DMSO in the assays (1 % v/v) does not substantially affect the activity of the PDEs investigated. After a preincubation of 5 min at 37°C, the reaction is started by adding the substrate (cAMP) and the assays are incubated for a further 15 min; after that, they are stopped by adding SPA beads (50 μl). In accordance with the manufacturer's instructions, the SPA beads had previously been resuspended in water, but were then diluted 1:3 (v/v) in water; the diluted solution also contains 3 mM IBMX to ensure a complete PDE activity stop. After the beads have been sedimented (> 30 min), the MTP's are analyzed in commercially available luminescence detection devices. The corresponding IC₅₀ values of the compounds for the inhibition of PDE activities are determined from the concentration-effect curves by means of non-linear regression.

The inhibitory values determined for the compounds according to the invention follow from the following Table 1, in which the numbers of the compounds correspond to the numbers of the examples.

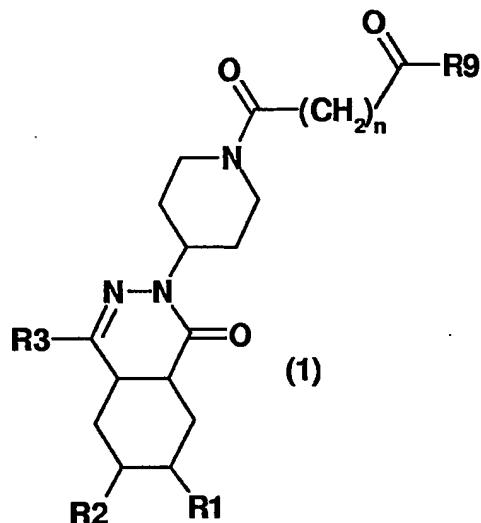
The inhibitory values of the compounds 1-6 have been determined according to Method A. The inhibitory values of the compounds 7-15 have been determined according to Method B.

Table 1**Inhibition of PDE4 activity [measured as -logIC₅₀ (mol/l)]**

Compound	PDE4 Inhibition
1	9.6
2	10.0
3	10.3
4	9.8
5	8.9
6	9.7
7	9.1
8	10.2
9	9.8
10	9.8
11	9.2
12	9.7
13	8.4
14	9.1
15	10.4

Patent claims

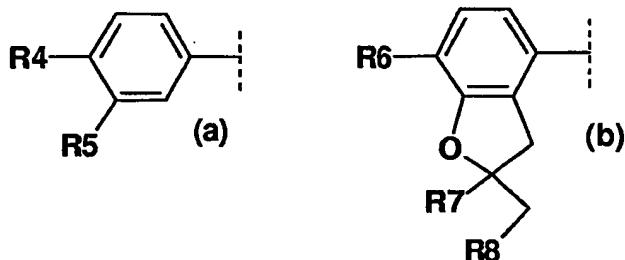
1. Compounds of formula 1



in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is hydroxyl, 1-4C-alkoxy, -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,

R10 is hydroxyl, 1-4C-alkoxy or 1-4C-alkoxy-2-4C-alkyl,

R11 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R12 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R13 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R14 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



wherein

A is O, S, SO, SO₂ or NR15,

R15 is hydrogen, 1-4C-alkyl, phenyl, pyridyl, -(CH₂)_m-R16 or -(CH₂)_p-C(O)R17,

R16 is -N(R18)R19,

R17 is -N(R20)R21,

R18 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R19 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-,

4-morpholinyl-, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring,

R20 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R21 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-,

4-morpholinyl, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring,

n is 0, 2, 3 or 4,

m is 2, 3 or 4,

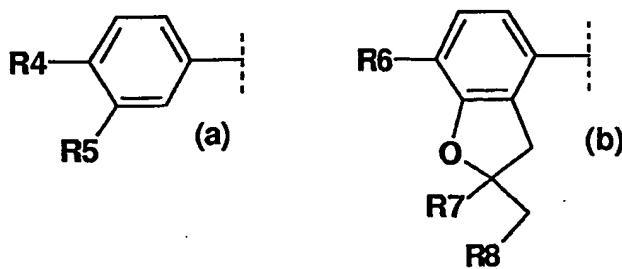
p is 1, 2, 3 or 4,

and the salts of these compounds.

2. Compounds of formula 1 according to claim 1, in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and **R8** together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is 1-4C-alkoxy, -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,

R10 is hydroxyl, 1-4C-alkoxy or 1-4C-alkoxy-2-4C-alkyl,

R11 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R12 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R13 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R14 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or **R13** and **R14** together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



wherein

A is O, S, SO, SO₂ or NR15,

R15 is hydrogen, 1-4C-alkyl, phenyl, pyridyl, -(CH₂)_m-R16 or -(CH₂)_p-C(O)R17,

R16 is -N(R18)R19,

R17 is -N(R20)R21,

R18 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

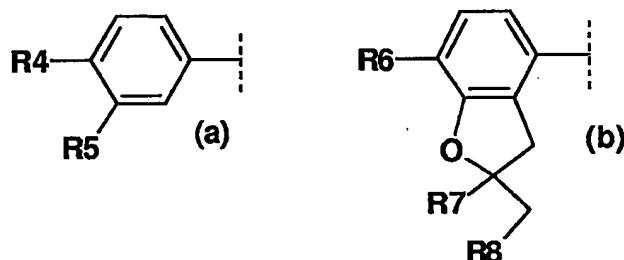
R19 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-, 4-morpholinyl-, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring, R20 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl, R21 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl, or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a 1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-, 4-morpholinyl, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring, n is 0, 2, 3 or 4, m is 2, 3 or 4, p is 1, 2, 3 or 4, and the salts of these compounds.

3. Compounds of formula 1 according to claim 1, in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is 1-4C-alkoxy, -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,

R10 is hydroxyl, 1-4C-alkoxy or 1-4C-alkoxy-2-4C-alkyl,

R11 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R12 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,
 R13 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,
 R14 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,
 or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a
 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



wherein

A is O, S, SO, SO₂ or NR15,

R15 is hydrogen, 1-4C-alkyl, phenyl, pyridyl, -(CH₂)_m-R16 or -(CH₂)_p-C(O)R17,

R16 is -N(R18)R19,

R17 is -N(R20)R21,

R18 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R19 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-,

4-morpholinyl-, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring,

R20 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R21 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-,

4-morpholinyl-, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring,

n is 2, 3 or 4,

m is 2, 3 or 4,

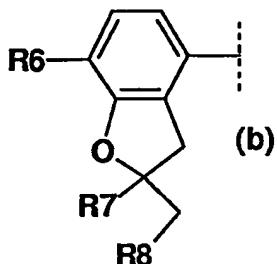
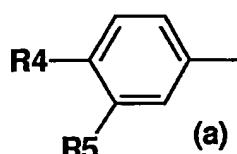
p is 1, 2, 3 or 4,

and the salts of these compounds.

4. Compounds of formula 1 according to claim 1, in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,

R9 is -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,

R10 is hydroxyl or 1-4C-alkoxy,

R11 is hydrogen or 1-4C-alkyl,

R12 is hydrogen or 1-4C-alkyl,

R13 and R14 are identical and are hydrogen or 1-4C-alkyl,

or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



wherein

A is O, S or NR15,

R15 is hydrogen, 1-4C-alkyl or -(CH₂)_p-C(O)R17,

R17 is -N(R20)R21,

R20 is hydrogen or 1-4C-alkyl,

R21 is hydrogen or 1-4C-alkyl,

or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-, 4-morpholinyl or 4-thiomorpholinyl-ring,

n is 2,

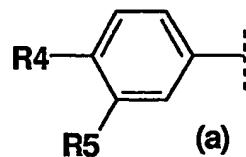
p is 1,

and the salts of these compounds.

5. Compounds of formula 1 according to claim 1, in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formula (a)



wherein

R4 is methoxy or ethoxy,
 R5 is methoxy or ethoxy,
 R9 is $-\text{N}(\text{R13})\text{R14}$,
 R13 is hydrogen,
 R14 is hydrogen,
 or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a ring of formula (c),

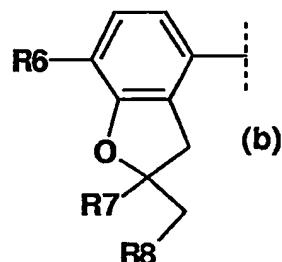
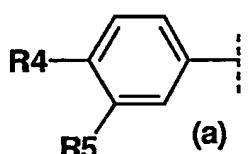


wherein

A is O or NR15,
 R15 is methyl or $-(\text{CH}_2)_p\text{-C}(\text{O})\text{R17}$,
 R17 is 1-pyrrolidinyl,
 n is 2,
 p is 1,

and the salts of these compounds.

6. Compounds of formula 1 according to claim 1, in which
 R1 and R2 are both hydrogen or together form an additional bond,
 R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is hydroxyl, 1-4C-alkoxy, -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,

R10 is hydroxyl, 1-4C-alkoxy or 1-4C-alkoxy-2-4C-alkyl,

R11 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R12 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R13 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R14 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



wherein

A is O, S, SO, SO₂ or NR15,

R15 is hydrogen, 1-4C-alkyl, phenyl, pyridyl, -(CH₂)_m-R16 or -(CH₂)_p-C(O)R17,

R16 is -N(R18)R19,

R17 is -N(R20)R21,

R18 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R19 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-,

4-morpholinyl-, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring,

R20 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R21 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-,

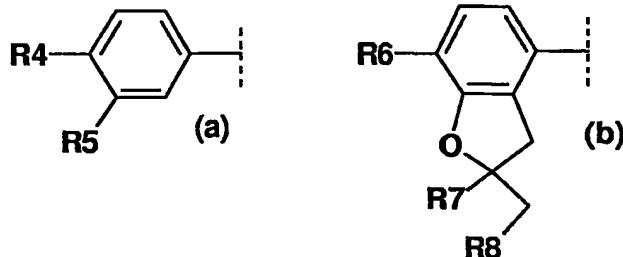
4-morpholinyl, 4-thiomorpholinyl-, thiomorpholin-1-oxide-4-yl- or thiomorpholin-1,1-dioxide-4-yl-ring,

n is 0,

m is 2, 3 or 4,

p is 1, 2, 3 or 4,
and the salts of these compounds.

7. Compounds of formula 1 according to claim 1, in which
R1 and R2 are both hydrogen or together form an additional bond,
R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,

R9 is -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,

R10 is hydroxyl, 1-4C-alkoxy or 1-4C-alkoxy-2-4C-alkyl,

R11 is hydrogen or 1-4C-alkyl,

R12 is hydrogen or 1-4C-alkyl,

R13 is hydrogen or 1-4C-alkyl,

R14 is hydrogen or 1-4C-alkyl,

or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepinyl-ring or a ring of formula (c),



wherein

A is O, S or NR15,

R15 is hydrogen, 1-4C-alkyl or -(CH₂)_p-C(O)R17,

R17 is -N(R20)R21,

R20 is hydrogen or 1-4C-alkyl,

R21 is hydrogen or 1-4C-alkyl,

or R20 and R21 together and with inclusion of the nitrogen atom to which they are bonded, form a

1-pyrrolidinyl-, 1-piperidinyl-, 1-piperazinyl, 1-(1-4C-alkyl)-piperazin-4-yl-, 1-hexahydroazepinyl-,

4-morpholinyl or 4-thiomorpholinyl-ring,

n is 0,

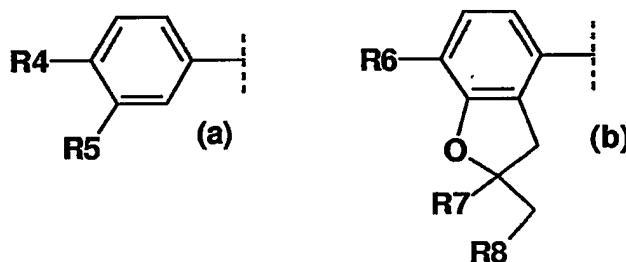
p is 1,

and the salts of these compounds.

8. Compounds of formula 1 according to claim 1, in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is methoxy or ethoxy,

R5 is methoxy or ethoxy,

R6 is methoxy,

R7 is methyl and

R8 is hydrogen,

R9 is -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,

R10 is hydroxyl or methoxyethyl,

R11 is methyl,

R12 is methyl,

R13 is hydrogen or methyl,

R14 is hydrogen or methyl,

or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a ring of

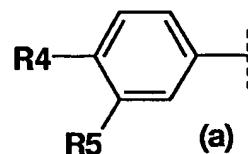
formula (c),



wherein

A is O or NR15,
 R15 is methyl,
 n is 0,
 and the salts of these compounds.

9. Compounds of formula 1 according to claim 1, in which
 R1 and R2 are both hydrogen or together form an additional bond,
 R3 represents a phenyl derivative of formula (a)



wherein

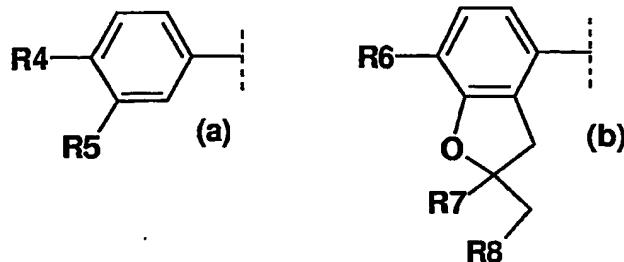
R4 is methoxy or ethoxy,
 R5 is methoxy or ethoxy,
 R9 is -N(R10)H, -N(H)N(R11)R12 or -N(R13)R14,
 R10 is hydroxyl or methoxyethyl,
 R11 is methyl,
 R12 is methyl,
 R13 is hydrogen or methyl,
 R14 is hydrogen or methyl,
 or R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a ring of formula (c),



wherein

A is O or NR15,
 R15 is methyl,
 n is 0,
 and the salts of these compounds.

10. Compounds of formula 1 according to claim 1, in which
 R1 and R2 are both hydrogen or together form an additional bond,
 R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is methoxy or ethoxy,
 R5 is methoxy or ethoxy,
 R6 is methoxy,
 R7 is methyl and
 R8 is hydrogen,
 R9 is $-\text{N}(\text{R13})\text{R14}$,
 R13 and R14 together and with inclusion of the nitrogen atom to which they are bonded, form a ring of formula (c),



wherein

A is O,

n is 0,

and the salts of these compounds.

11. Compounds of formula 1 according to any of the claims 1 to 10, in which the absolute configuration (according to the rules of Cahn, Ingold and Prelog) is S in the position 4a and R in the position 8a.
12. Compounds of formula 1 according to claim 1 for use in the treatment of diseases.
13. Pharmaceutical compositions containing one or more compounds of formula 1 according to claim 1 together with the usual pharmaceutical auxiliaries and/or carrier materials.
14. Use of compounds of formula 1 according to claim 1 for the preparation of pharmaceutical compositions for the treatment of airway disorders.

15. A method for treating an illness treatable by the administration of a PDE4 inhibitor in a patient comprising administering to said patient in need thereof a therapeutically effective amount of a compound of formula 1 as claimed in claim 1.
16. A method for treating airway disorders in a patient comprising administering to said patient a therapeutically effective amount of a compound of formula 1 as claimed in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2005/050417

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D401/04 C07D401/14 A61K31/498 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHEDMinimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/064584 A (BYK GULDEN LOMBERG CHEM FAB ; GUTTERER BEATE (DE); GRUNDLER GERHARD (D) 22 August 2002 (2002-08-22) cited in the application Abstract; claims; examples, e.g. no. 4.	1-16

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *'A' document defining the general state of the art which is not considered to be of particular relevance
- *'E' earlier document but published on or after the International filing date
- *'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *'O' document referring to an oral disclosure, use, exhibition or other means
- *'P' document published prior to the international filing date but later than the priority date claimed

- *'T' later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- *'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

- *'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

- *'&' document member of the same patent family

Date of the actual completion of the International search

27 June 2005

Date of mailing of the International search report

04/07/2005

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+31-70) 340-3016

Authorized officer

Weisbrod, T

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/050417

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 15 and 16 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 6 and 11-16 (all part)

directed to compounds (1) wherein R9 = OH and n = 0, as well as subject matter referring to such compounds (1);

2. claims: 1-3, 6, and 11-16 (all part)

directed to compounds (1) wherein R9 = 1-4C-alkoxy, as well as subject matter referring to such compounds (1);

3. claims: 1-3, 6, 11-16 (all part) and 4, 5, 7-10 (all complete)

directed to compounds (1) wherein R9 = NHR10, NR13R14 or NH-NR11R12, as well as subject matter referring to such compounds (1).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2005/050417

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 02064584	A 22-08-2002	BG	108124 A	31-08-2004
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		ZA	200306815 A	17-06-2004